STATE OF PENNSYLVANIA §

COUNTY OF PHILADELPHIA §

AFFIDAVIT OF ARTHUR L. FRANK, MD, PhD.

I am a Physician and Professor of Public Health at Drexel University where I hold the position of Chair of Environmental & Occupational Health. I am also a Professor of Medicine at the Drexel University College of Medicine. I am a Board Certified medical doctor, having received my medical degree in 1972, from the Mt. Sinai School of Medicine. I have been Board Certified by the National Board of Medical Examiners since 1973, have been a Diplomat of the American Board of Internal Medicine since 1978 and with the American Board of Preventive Medicine (Occupational Medicine) since 1979. I received my Ph.D. in 1977 from the City University of New York, where I studied in its Biomedical Sciences Doctoral Program. My current CV is attached hereto. I have provided expert opinion, in numerous jurisdictions, on the causation between asbestos exposure and the development of mesothelioma.

I hold the following opinions to a reasonable degree of medical and scientific certainty:

1. There is overwhelming, generally accepted evidence that inhalation of asbestos fibers of any type, from any source or product, causes mesothelioma (in all known locations), lung cancer, asbestosis, pleural plaques, and other cancers. I joined fifty-one (51) scientists in expressing my opinions about the hazards of asbestos in the article by Welch, et al[1], entitled *Asbestos exposure causes mesothelioma, but not this asbestos exposure: an amicus brief to the Michigan Supreme Court*. I continue to hold the opinions set forth in that published paper, along with the other opinions expressed here, to a reasonable degree of medical and scientific certainty.

2. Outside the courtroom, there is little or no dispute in the medical literature that all asbestos fiber types, including chrysotile, cause asbestosis, lung cancer, and pleural plaques/thickening. The methodology and bases for the opinions as stated herein are not novel and for the reasons set forth are generally accepted in the medical and scientific community.

3. There are numerous occupational epidemiology, registry and case studies clearly linking all types of asbestos, including chrysotile asbestos, to pleural and peritoneal mesothelioma[2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16].

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[1] Welch, et al, *Asbestos exposure causes mesothelioma, but not this asbestos exposure: an amicus brief to the Michigan Supreme Court*. Int J Occup Environ Health 13:318–327 (2007) (a copy is attached hereto)

[2] Kanarek, *Mesothelioma from Chrysotile Asbestos: Update*, AEP Vol. 21, No. 9, pp. 688-97 (2011).

[3] Hein et al, *Follow-up study of chrysotile textile workers: Cohort mortality and exposure-response*. Occup Environ Med. 64:616–625 (2007)

[4] Loomis et al, *Lung cancer mortality and fiber exposures among North Carolina asbestos textile workers*, Occup Environ Med. 66:535–542 (2009)

[5] Silverstein et al, *Developments in asbestos cancer risk assessment*, Am J Ind Med. 52:850–858 (2009);

4. "There is general agreement among scientists and health agencies . . . [e]xposure to any asbestos type (i.e., serpentine [chrysotile] or amphibole) can increase the likelihood of lung cancer, mesothelioma, and nonmalignant lung and pleural disorder[17]." Many other reviews support this conclusion, such as those from the American Conference of Governmental Industrial Hygienists,[18] the American Thoracic Society,[19] the Environmental Protection Agency,[20] the International Agency for Research on Cancer (IARC),[21,22] the National Toxicology Program,[23] the Occupational Safety and Health Administration,[24] the Consumer Products Safety Commission (CPSC),[25] the World Health Organization,[26,27,28] the Collegium Ramazzini,[29] and the World Trade Organization[30].

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[6] Finkelstein et al, *Mesothelioma among employees of a Connecticut factory that manufactured friction materials using chrysotile asbestos*, Ann Occup Hyg. 54:692–696 (2010)
[7] Egilman et al, *A case of occupational peritoneal mesothelioma from exposure to tremolite-free chrysotile in Quebec, Canada: A black swan case*. Am J Ind Med. 54:153–156 (2011)
[8] Pira et al, *Mortality from cancer and other causes in the Balangero cohort of chrysotile asbestos miners*, Occup Environ Med. 66:805–809 (2009)
[9] Mirabelli et al, *Excess of mesotheliomas after exposure to chrysotile in Balangero, Italy*, Occup Environ Med. 65:815–819 (2008)
[10] Turci et al, *Role of associated mineral fibres in chrysotile asbestos health effects: The case of Balangeroite*. Ann Occup Hyg.;53:491–497 (2009)
[11] Everatt et al, Occupational asbestos exposure among respiratory cancer patients in Lithuania. Am J Ind Med. 50:455–463 (2007)
[12] Madkour et al, *Environmental exposure to asbestos-response relationship with mesothelioma*, Eastern Mediterranean Health J. 15:25–38 (2009)
[13] Yano et al, *Mesothelioma in a worker who spun chrysotile asbestos at home during childhood*, Am J Ind Med.;52: 282–287 (2009)
[14] Baumann et al, *Pleural mesothelioma in New Caledonia: An acute environmental concern*, Cancer Detect Prev. 31:70–76 (2007)
[15] Baumann et al, *Pleural mesothelioma in New Caledonia: Associations with environmental risk factors*, Environ Health Perspect 119:695–700 (2011)
[16] Nishikawa et al, *Recent mortality from mesothelioma, historical patterns of asbestos use, and adoption of bans: A global assessment*. Environ Health Perspect. 116:1675–1680 (2008)
[17] U.S. Public Health Service, U.S. Department of Health & Human Services. Toxicological profile for asbestos. Atlanta: Agency for Toxic Substances and Disease Registry; (2001).
[18] American Conference of Governmental Industrial Hygienists. *Asbestos: TLV® Chemical Substances* 7th Edition Cincinnati OH: ACGIH; Report No.: Publication #7DOC-040 (2001).
[19] American Thoracic Society. *Diagnosis and initial management of nonmalignant diseases related to asbestos*. Am J Respir Crit Care Med;170(6):691-715 (Sep 15 2004).
[20] Environmental Protection Agency. *Airborne Asbestos Health Assessment Update. Springfield VA*: NTIS; Report No.: EPA/600/8-84/003F (1986).
[21] IARC. *Asbestos: Monograph on the Evaluation of Carcinogenic Risk to Man. Lyon: International Agency for Research on Cancer*; (1988).
[22] Straif K, et al. *A review of human carcinogens--part C: metals, arsenic, dusts, and fibres. Lancet Oncol*; 10(5):453-4 (May 2009).
[23] National Toxicology Program. *Report on Carcinogens, Eleventh Edition*. U.S. Department of Health and Human Services, Public Health Service; (2005).
[24] Occupational Safety and Health Administration. *Occupational exposure to asbestos; final rule*. Federal Register; 59:40964-1162 (1994).
[25] Consumer Product Safety Commission. CANCER HAZARD! CPSC Warns About Asbestos in Consumer Products: Safety Alert. Report No.: CPSC Document #5080 (1994).
[26] World Health Organization. *Environmental Health Criteria 203: Chyrsotile Asbestos. Geneva*: World Health Organization; (1998).

This scientific consensus is also reflected in the Consensus Report of the 1997 Helsinki Conference,[31] publications from the American Cancer Society,[32] and publications from the National Cancer Institute of the National Institutes of Health[33].

5. Most recently, IARC published an update on asbestos that concluded "all forms of asbestos (chrysotile, crocidolite, amosite, tremolite, actinolite, and anthophyllite) . . . cause[s] mesothelioma and cancer of the lung, larynx, and ovary. Also positive associations have been observed between exposure to all forms of asbestos and cancer of the pharynx, stomach, and colorectum[34]." After defining asbestos as the aforementioned group of fiberous minerals, IARC stated that the "causal association between mesothelioma and asbestos has been well established." *Id.* IARC also discussed some unresolved questions such as potential differences in relative potency by fiber type and the issues of fiber length. I follow the same weight-of-the-evidence methodology used by IARC, WHO and ATSDR among others, in reaching my conclusions about the health effects of asbestos.

Substantial Epidemiological Data Supports the Consensus that All Types of Asbestos Can Cause Mesothelioma in Humans

6. In addition to these consensus documents from national and international agencies, numerous peer-reviewed epidemiological studies, meta-analyses, reviews and reports also conclude that chrysotile asbestos causes mesothelioma[35].

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[27] World Health Organization. *Elimination of asbestos related diseases*. Ref Type: Generic (2006)

[28] World Health Organization. *Environmental Health Criteria 53: Asbestos and Other Natural Mineral Fibres*. Geneva: World Health Organization; (1986).

[29] Collegium Ramazzini, *Asbestos Is Still With Us: Repeat Call for a Universal Ban*, Am. J. Indust. Med. 54:168-173 (2011).

[30] World Trade Organization. European Communities – Measures Affecting Asbestos and Asbestos – Containing Products. Report No.: WT/DS135/R (2000).

[31] *Asbestos, asbestosis, and cancer: the Helsinki criteria for diagnosis and attribution*. Scand J Work Environ Health; 23(4):311-6 (Aug 1997).

[32] *Malignant Mesothelioma*. American Cancer Society. 10-19-2006.
Ref Type: Pamphlet (2006)

[33] National Cancer Institute. *Factsheet - Asbestos: Questions and Answers*. Bethesda MD, National Institutes of Health. Ref Type: Pamphlet (2003)

[34] IARC. Monograph 100C: *Asbestos (Chrysotile, Amosite, Crocidolite, Actinolite and Anthophyllite)*, Lyon: International Agency for Research on Cancer (2012)

[35] Kanarek, *Mesothelioma from Chrysotile Asbestos: Update*, AEP Vol. 21, No. 9, pp. 688-97 (2011); Elliott et al, *Lung cancer mortality in North Carolina and South Carolina chrysotile asbestos textile workers*, Occup Environ Med doi:10.1136 (2012); Li et al, *Cohort studies on cancer mortality among workers exposed only to chrysotile asbestos: a meta-analysis*, Biomed Environ Sci 17(4):459-468 (2004); Loomis et al, *Lung cancer mortality and fibre exposures among North Carolina asbestos textile workers*, Occ Env Med 66:535-542 (2009); Hein et al, *Follow-up study of chrysotile textile workers: Cohort mortality and exposure-response*. Occup Environ Med. 64:616–625 (2007); Silverstein et al, *Developments in asbestos cancer risk assessment*, Am J Ind Med. 52:850–858 (2009); Finkelstein et al, *Mesothelioma among employees of a Connecticut factory that manufactured friction materials using chrysotile asbestos*, Ann Occup Hyg. 54:692–696 (2010); Egilman et al, *A case of occupational peritoneal mesothelioma from exposure to tremolite-free chrysotile in Quebec, Canada: A black swan case*. Am J Ind Med. 54:153–156 (2011); Pira et al, *Mortality from cancer and other causes in the Balangero cohort of chrysotile asbestos miners*, Occup Environ

7. Prior risk assessments looking at the potency of the various fiber types used unreliable data about exposures and thus yielded unreliable data. A recent meta-analysis, using only epidemiological studies with more reliable data, yielded results which show that chrysotile is much more potent for causing mesothelioma than previously believed[36]. These authors recognize that "[a]sbestos is a well-known carcinogen responsible for cancer of the pleura and peritoneum (mesothelioma) and lung cancer. The profound consequence of historical exposure to asbestos is well documented in many countries. *Id.* (citing Lin et al., 2007)[37]. Using the more accurate measurements, the authors of this risk assessment recommended lowering the exposure limit to 0.002 f/cc or 2% of the current PEL (0.1 f/cc) set by OSHA in the United States.

8. IARC's recent update on the carcinogenicity of asbestos points out the weaknesses, limitations and incomplete nature of two risk assessments, Berman et al (2003 and 2008) and Hodgson et al, (2000), that suggested large potency differences between amphibole forms of asbestos and chrysotile[38]. IARC pointed out that neither Berman et al (2003 and 2008) nor Hodgson et al, (2000) considered the important data on chrysotile potency data from Loomis et al (2009) and Mirabelli et al (2008). IARC also noted that "there is a high

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Med. 66:805–809 (2009); Mirabelli et al, *Excess of mesotheliomas after exposure to chrysotile in Balangero, Italy,* Occup Environ Med. 65:815–819 (2008); Turci et al, *Role of associated mineral fibres in chrysotile asbestos health effects: The case of Balangeroite.* Ann Occup Hyg.;53:491–497 (2009); Everatt et al, Occupational asbestos exposure among respiratory cancer patients in Lithuania. Am J Ind Med. 50:455–463 (2007); Madkour et al, *Environmental exposure to asbestos-response relationship with mesothelioma*, Eastern Mediterranean Health J. 15:25–38 (2009); Yano et al, *Mesothelioma in a worker who spun chrysotile asbestos at home during childhood*, Am J Ind Med.;52: 282–287 (2009); Baumann et al, *Pleural mesothelioma in New Caledonia: An acute environmental concern*, Cancer Detect Prev. 31:70–76 (2007); Baumann *et al, Pleural mesothelioma in New Caledonia: Associations with environmental risk factors*, Environ Health Perspect 119:695–700 (2011); Nishikawa et al, *Recent mortality from mesothelioma, historical patterns of asbestos use, and adoption of bans: A global assessment.* Environ Health Perspect. 116:1675–1680 (2008); Welch et al, *Asbestos and peritoneal mesothelioma among college-educated men*, Int J Occup Environ Health, 11: 254–258 (2005); Lemen, *Asbestos in brakes: exposure and risk of disease*, Am J Ind Med 2004; 45(3):229-237 (2004); Frank et al, *Carcinogenic implications of the lack of tremolite in UICC reference chrysotile.* Am J Ind Med 34(4):314-317 (1998); Smith et al, *Chrysotile asbestos is the main cause of pleural mesothelioma*, Am J Ind Med 30:252-266 (1996); Cullen, *Chrysotile asbestos: enough is enough*, Lancet 351(9113):1377-1378 (1998); Landrigan et al, *The hazards of chrysotile asbestos: a critical review.* Ind Health 37(3):271-280 (1999); Landrigan et al, *Collegium Ramazzini call for an international ban on asbestos*, Am J Ind Med 47(6):471-474 (2005); Stayner et al, *Occupational exposure to chrysotile asbestos and cancer risk: a review of the amphibole hypothesis*, Am J Public Health 86:179-186(1996).

[36] Burdorf et al, *Applying Quality Criteria to Exposure in Asbestos Epidemiology Increases the Estimated Risk*, Ann. Occup. Hyg., Vol. 55, No. 6, pp. 565–568 (2011) (discussing Gezondheidsraad, *Asbestos—risks of environmental and occupational exposure*, The Hague, the Netherlands: Health Council of the Netherlands, report 2010/10E (2010). Available at www.gezondheidsraad.nl/en/publications/asbestos-risks-environmental-and-occupational-exposure. Accessed March 28, 2012)

[37] Lin et al. *Ecological association between asbestos-related diseases and historical asbestos consumption: an international analysis*, Lancet; 369: 844–9 (2007)

[38] IARC. Monograph 100C: *Asbestos (Chrysotile, Amosite, Crocidolite, Actinolite and Anthophyllite)*, Lyon: International Agency for Research on Cancer (2012) (discussing Berman et al, *Update of potency factors for asbestos-related lung cancer and mesothelioma, Crit Rev Toxicol,* 38: Suppl 11–47 (2008) and Hodgson et al, *The quantitative risks of mesothelioma and lung cancer in relation to asbestos exposure*, Ann Occup Hyg, 44: 565–601 (2000).

degree of uncertainty concerning the accuracy of the relative potency estimates derived from the Hodgson & Darnton and Berman & Crump analyses because of the severe potential for exposure misclassification in these studies." Significantly, IARC also found that the "Berman & Crump meta-analyses provided weak evidence that fibre length is a determinant of the potency of asbestos." Others believe that the disparity in results and methods renders quantitative risk assessments like these unreliable[39]. The lack of reliable exposure data for most of the historic cohorts of asbestos exposed workers was a fundamental reason why the EPA abandoned its attempt to develop a "bin-specific" model for quantifying the danger of various types and sizes of asbestos fibers[40]. It is my opinion that all forms of asbestos cause mesothelioma, that the fibers of all lengths contribute to the risk of disease and that the existing data is insufficient to *quantify* any differences in the relative potency of the types of asbestos for causing disease.

All Types of Asbestos Cause Lung Cancer and Asbestosis

9. Recently, Loomis et al (2010) reported on four textile plants using chrysotile asbestos that have shown an increased risk of both asbestosis and lung cancer, and the incidence of both diseases increased with increasing dose of asbestos[41]. The Agency for Toxic Substances and Disease Registries (ATSDR) "assess[ed] all relevant toxicologic testing and information that has been peer reviewed" and concluded in its 2001 Toxicological Profile on Asbestos that "[a]vailable evidence indicates that all asbestos fiber types are fibrogenic[42]". The American Thoracic Society (ATS) also concluded in its 2004 statement *Diagnosis and Initial Management of Non-Malignant Disease Related to Asbestos* that all fiber types can cause lung fibrosis (asbestosis)[43]. Loomis et. al. also measured excess incidence of mesotheliomas among the various plants, including when plants that did not use commercial amphibole were excluded from the analysis.

10. Toxicological data reinforces the conclusions discussed above based upon epidemiological studies of all forms. ATSDR also concluded "There is little doubt that all types of asbestos can cause lung cancer. For example, statistically significant increases in lung

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[39] Elliott et al, *Lung cancer mortality in North Carolina and South Carolina chrysotile asbestos textile workers*, Occup Environ Med doi:10.1136 (2012) (citing Greenland, *Meta-analysis*. In: Rothman KJ, Greenland S, Lash TL. Modern Epidemiology. 3rd ed. Philadephia: Lippincott Williams & Wilkins, 652e82 (2008) for proposition that "the strong heterogeneity between cohorts underscores the potential differences between them and suggests a single estimate of effect may not be possible.").

[40] Silverstein et al, *Developments in asbestos cancer risk assessment*, Am J Ind Med. 52:850–858 (2009); Johnson S. 2008. Letter from Stephen L. Johnson, EPA Administrator to Dr. Agnes Kane, Chair of Science Advisory Board Asbestos Committee. 12/29/2009.

[41] Loomis D, Dement J, Richardson D, Wolf S. Asbestos fibre dimensions and lung cancer mortality among workers exposed to chrysotile. Occup Environ Med 2010 Sep;67(9):580-4.

[42] U.S.Public Health Service, U.S.Department of Health & Human Services. Toxicological profile for asbestos. Atlanta: Agency for Toxic Substances and Disease Registry; 2001.

[43] American Thoracic Society. *Diagnosis and initial management of nonmalignant diseases related to asbestos*. Am J Respir Crit Care Med;170(6):691-715 (Sep 15 2004).

cancer mortality have been reported in workers exposed primarily to chrysotile[44]". The International Agency for Research on Cancer (IARC) has also concluded that chrysotile asbestos causes lung cancer in humans[45]. A recent meta-analysis by Li reaches the same conclusion[46]. Analysis of a chrysotile cohort in China also confirmed "that exposure to chrysotile asbestos is associated with an increased risk of death from lung cancer and asbestosis, and shows a clear exposure response relationship[47]." Asbestos may be more potent for causing lung cancer than some previously thought[48]. The evidence shows that even low level exposures to asbestos causes a substantial number of lung cancers in occupationally exposed workers[49].

Other Medical and Scientific Evidence that All Types of Asbestos Cause Mesothelioma

11. In addition to the extensive reliable epidemiological evidence that all types of asbestos cause mesothelioma in humans, there is substantial other evidence from animal studies that supports my opinion that all types of asbestos cause mesothelioma in humans. Lung cancer and mesothelioma have been found in rats in inhalation studies. Although the results vary, at least one study, Wagner et al (1974) found chrysotile caused as many cancers as crocidolite[50]. Proper scientific inquiry requires consideration of all forms of animal studies regarding asbestos exposure, including, inhalation, instillation and injection studies. While each of these types of studies has limitations, they also have strengths and must be considered. This is no different than the strengths and limitations of various types of epidemiological studies or, for that matter, all types of scientific evidence.

12. Numerous animal studies have demonstrated all forms of asbestos cause mesothelioma using both intrapleural and intraperitoneal injection[51]. Studies exposing animals via

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[44] U.S.Public Health Service, U.S.Department of Health & Human Services. Toxicological profile for asbestos. Atlanta: Agency for Toxic Substances and Disease Registry; 2001.
[45] IARC. *Asbestos: Monograph on the Evaluation of Carcinogenic Risk to Man. Lyon: International Agency for Research on Cancer*; (1988).
[46] Li L, Sun TD, Zhang X, Lai RN, Li XY, Fan XJ, et al. Cohort studies on cancer mortality among workers exposed only to chrysotile asbestos: a meta-analysis. Biomed Environ Sci 2004 Dec;17(4):459-68
[47] Deng et al, *Exposure-response relationship between chrysotile exposure and mortality from lung cancer and asbestosis*, Occup Environ Med (2011).

[48] Gustavsson, *Low-Dose Exposure to Asbestos and Lung Cancer: Dose-Response Relations and Interaction with Smoking in a Population-based Case-Referent Study in Stockholm, Sweden, Am J Epidemiol* 155 (11) (2002).

[49] De Matteis et al, *Impact of occupational carcinogens on lung cancer risk in a general population*, Int. J. Epidemiol. Advance Access (published March 31, 2012).

[50] IARC. Monograph 100C: *Asbestos (Chrysotile, Amosite, Crocidolite, Actinolite and Anthophyllite)*, Lyon: International Agency for Research on Cancer (2012) (discussing Wagner et al, *The effects of the inhalation of asbestos in rats*. Br J Cancer, 29: 252–269 (1974)).

[51] Wagner, *Experimental production of mesothelial tumours of the pleura by implantation of dusts in laboratory animals*, Nature, 196: 180–181 (1962); Wagner et al, *Mesotheliomas in rats following inoculation with asbestos*, Br J Cancer, 23: 567–581 (1969); Pott et al, *Relevance of non-physiologic exposure routes for carcinogenicity studies of solid particles*. In: Toxic and Carcinogenic Effects of Solid Particles in the Respiratory Tract. 4th International

intratracheal administration have shown that asbestos fibers induced lung tumors in rats, and lung tumors and mesotheliomas in hamsters[52].

13. At least one animal study, Kogan et al (1987), demonstrated peritoneal mesothelioma in rats exposed to high doses of chrysotile asbestos via intragastric administration[53]. Tumors were seen in 18 of 75 exposed rats, between 18–30 months after the beginning of the experiment, including two peritoneal mesotheliomas, eight gastric adenomas, two gastric adenocarcinomas, one gastric carcinoma, one cancer of the forestomach, one small intestine adenocarcinoma, and three abdominal lymphoreticular sarcomas. No tumors were observed in 75 control animals.

14. Studies of asbestos-exposed pets have also confirmed a relationship between environmental exposure to asbestos and mesothelioma. A case control study showed an 8 fold (statistically significant) increased risk of mesothelioma in dogs with asbestos exposures as compared to those without asbestos exposure[54].

15. In an article by Gemba, et al,[55] a significant number of mesotheliomas, both pleural and peritoneal, were found in the automobile manufacturing industry. As the article points out, friction materials and other automobile products contain predominantly chrysotile. This further supports the conclusion that chrysotile exposure gives rise to multiple types of mesothelioma.

16. This conclusion is supported by experimental data that shows that chrysotile is transported to the pleural and peritoneum, and animal experiments showing development of lung fibrosis and lung cancer. Suzuki demonstrated that chrysotile is preferentially transported to mesothelial tissues like the pleural space, while amosite is more likely to be retained in the lung itself[56]. Fiber studies also show that asbestos, including chrysotile, is also

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Inhalation Symposium Hanover 1 - 5 March, 1993. Mohr U, editor. Washington, D.C: ILSI-Press, pp. 109–125 (1993); Stanton et al, *Relation of particle dimension to carcinogenicity in amphibole asbestoses and other fibrous minerals*, J Natl Cancer Inst, 67: 965–975 (1981).

[52] Pott et al, *Carcinogenicity studies on fibres, metal compounds, and some other dusts in rats*, Exp Pathol, 32: 129–152 (1987); Smith et al, *Long-term health effects in hamsters and rats exposed chronically to man-made vitreous fibres*, Ann Occup Hyg, 31: 4B731–754 (1987); Pott et al, *Lung carcinomas and mesotheliomas following intratracheal instillation of glass fibres and asbestos*. In: Proceedings of the VIth International Pneumoconiosis Conference 20–23 September 1983. Bochum, Germany: International Labour Office, pp. 746–756 (1984).

[53] Kogan et al, *Possibility of inducing glandular cancer of the stomach in rats exposed to asbestos*, Br J Ind Med, 44: 682–686 (1987). Given the shorter lifespan of rats as compared to humans, high doses of potential carcinogens are often used to evaluate the carcinogenic potential of a substance.

[54] Glickman et al, *Mesothelioma in pet dogs associated with exposure of their owners to asbestos*, Environ Res, 32: 305–313 (1983)

[55] Gemba, et al, *National survey of malignant mesothelioma and asbestos exposure in Japan*, Cancer Sci. 103 (3):483 – 90 (2012)

[56] Suzuki. *Asbestos tissue burden study on human malignant mesothelioma*. Ind Health; 39(2):150-60 (Apr 2001).

transported to the peritoneum. Fibrosis has been produced in animals by inhalation or by intratracheal exposure to chrysotile[57]. In addition, studies in animals have reported increased incidence of lung cancer following chronic inhalation exposure to chrysotile[58,59]. Exposure to chrysotile fibers less than 5 microns in length (short fibers) is reported to increase the incidence of lung cancer, with a dose-response relationship[60]. The animal data strongly suggest that chrysotile asbestos fibers themselves, rather than amphibole contamination alone, plays a role in causing mesothelioma[61]. The data do not support a claim that fibers less than 5 microns are inert or non-potent nor was the adoption of the 5 micron length cut-off for NIOSH/OSHA measurements based upon any conclusion that fibers less than 5 microns in length are harmless[62,63]. Indeed, NIOSH made clear the 5 micron counting protocol was a method of convenience because it used a readily available microscope and that it was "*only an index of total fiber exposure and does not imply that shorter fibers do not pose a health hazard*[64]".

17. Other relevant data on the ability of asbestos to cause human cancer include toxicokinetics (routes of exposure), deposition, clearance, and translocation in humans, Molecular pathogenesis, and mechanisms of carcinogenesis.

18. Substantial evidence shows that asbestos fibers of all types can be inhaled deeply into the lung due to their aerodynamic qualities. Once in the lung, asbestos fibers of all types may also interact with lung epithelial cells, penetrate into the interstitium, and translocate to the pleura and peritoneum or more distant sites. Fibers that are not efficiently cleared or altered by physicochemical process (e.g. breakage, splitting, or chemical modification) are termed bio-persistent in the tissue where they are found. Many animal studies have looked a bio-persistence of asbestos is various tissues. As discussed above, while animal studies are important scientific evidence, it is important to be cautious when interpreting the data from such studies, due to methodological issues and differences between species[65]. As a recent review observed, "[t]he relevance of bio-persistence to [malignant mesothelioma]

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[57] O'Neill et al, *Lung Volume Changes in Rats Exposed to Chrysotile Asbestos*, Am. Rev. Respiratory Disease 123 (4) 146 (1981) ("Interstitial fibrosis was seen histologically in all exposed animals after one year and increased in severity during the year in air"). Purportedly tremolite-free Union Carbide brand asbestos produced similar results with less than half the dose.

[58] IARC. *Asbestos: Monograph on the Evaluation of Carcinogenic Risk to Man. Lyon: International Agency for Research on Cancer*; (1988).

[59] World Health Organization. *Environmental Health Criteria 203: Chyrsotile Asbestos. Geneva*: World Health Organization; (1998).

[60] Stayner, et al. *An epidemiological study of the role of chrysotile asbestos fibre dimensions in determining respiratory disease risk in exposed workers*. Occup Environ Med; 65(9):613-9 (Sep 2008).

[61] Frank et al., *Carcinogenic Implications of the Lack of Tremolite in UICC Reference Chrysotile*, AM. J. IND. MED. 34:314-317 (1998)

[62] Lemen, *Asbestos in brakes: exposure and risk of disease*, Am J Ind Med 2004; 45(3):229-237 (2004)

[63] Dodson et al, *Asbestos Fiber Length as Related to Potential Pathogenicity: A Critical Review*, Am. J. Indust Med 44:291–297 (2003).

[64] NIOSH, Revised Recommended Asbestos Standard, DWEW (NIOSH) Publication No. 77-169 (December 1976) (emphasis added).

[65] IARC *Man-made vitreous fibres*, IARC Monogr Eval Carcinog Risks Hum, 81: 1–381 (2002).

in humans has also been questioned. Due to the prolonged latency associated with mesothelioma, the absence of fibres at autopsy, some 40 years after first exposure, is hardly surprising[66]." These authors also cautioned regarding potential biases that can be interjected into animal models by preparation of samples etc.

19. While many investigators have looked at asbestos content in the lungs, lung asbestos content is less relevant to questions of mesothelioma causation than it is to questions of asbestosis and lung cancer causation; mesothelioma occurs in the mesothelial tissues around the lungs (pleura), the abdomen (peritoneum), heart (pericardium) and sex organs (tunica vaginalis)[67]. Numerous investigators have looked at tissue beyond the lungs and

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[66] Linton et al, *The ticking time-bomb of asbestos: Its insidious role in the development of malignant mesothelioma*, Critical Reviews in Oncology/Hematology xxx (2012) xxx–xxx (in press).

[67] *See, e.g.*, Warnock et al, *Asbestos Burden and the Pathology of Lung Cancer*, CHEST; 89:20-26 (1986) ('the pulmonary asbestos burden is probably not an accurate indicator of the degree of asbestos exposure"); Sebastien et al., *Asbestos Retention in Human Respiratory Tissues: Comparative Measurements in Lung Parenchyma and in Parietal Pleura*, in Biological Effects of Mineral Fibres, VOL. 1 Wagner, J.C., ed. (1980) (a lung asbestos count "is not a good indicator of pleural retention"); Suzuki et al., *Asbestos fibers and human malignant mesothelioma*, in Advances in the Prevention of Occupational Respiratory Diseases, Chiyotani, Hosoda, Aizawa, eds. (1998) (arguing that "asbestos fibers in the lung do not fully represent a total picture of asbestos exposure because translocated asbestos fibers are not retained in the lung."); Suzuki et al, *Asbestos Tissue Burden Study on Human Malignant Mesothelioma*, Ind. Health 2001, 39, 150-60 (questioning the adequacy of approach of "researchers have been focusing almost exclusively on asbestos fibers in the lung tissue"); Dodson et al., 2008, *A Technical Comparison of Evaluating Asbestos Concentration by Phase-Contrast Microscopy (PCM), Scanning Electron Microscopy (SEM), and Analytical Transmission Electron Microscopy (ATEM) as Illustrated From Data Generated From a Case Report*, INHALATION TOXICOLOGY, 20:723-732, (2008) (questioning the approach of looking at the lung when pleural or peritoneal cancer is at issue because "[w]ith respect to cancer, the concentration of asbestos at the site where the tumor starts is thought to be the most important factor in determining causation. It is impossible to know how much asbestos it takes to produce an asbestos-induced disease."); Finkelstein, *Asbestos Fibre Concentrations in the Lungs of Brake Workers: Another Look*, Ann. Occup. Hyg. 52(6):455-461 (2008) (explaining that "[s]ince chrysotile is cleared from the lungs of brake workers, tremolite is arguably a better marker of exposure to Quebec chrysotile than is chrysotile itself"); Kohyama et al, *Analysis of Asbestos Fibers in Lung Parenchyma, Pleural Plaques, and Mesothelioma Tissues of North American Insulation Workers*, 643 Ann. N.Y. Acad. Sci. 27 (1991) (stating that "[d]espite the absence of high concentrations of chrysotile fibers in the lung, significant accumulation of chrysotile fibers in pleural and peritoneal tissues should be considered a potentially important factor in the induction of human malignant mesothelioma"); Baker, *Limitations in Drawing Etiologic Inferences Based on Measurement of Asbestos Fibers from Lung Tissue*, 643 Ann. N.Y. Acad. Sci. 61 (1991) (discussing the many problems with fiber burden analysis and criticizing fiber burden analysis as inadequate to estimate past exposures); McDonald et al, *The epidemiology of mesothelioma in historical context*, Eur. Respir. J. 9, 1932-1942, 1938 (1996) (discussing the potential problems and "substantial questions" of fiber burden analyses); Dufresne et al., *Fibers in Lung Tissues of Mesothelioma Cases Among Miners and Millers of the Township of Asbestos, Quebec*, Am J. Ind. Med. 27:581-592, 587 (1995) (explaining that "[b]ecause of the relatively low durability of chrysotile asbestos in lung tissues, it is difficult if not impossible to relate chrysotile lung content to asbestos-related diseases in humans"); Frank et al., *Carcinogenic Implications of the Lack of Tremolite in UICC Reference Chrysotile*, Am. J. Ind. Med. 34:314-317 (1998).

found asbestos, predominantly chrysotile, in people with mesothelioma. Studies confirm that asbestos fibers are biopersistent and accumulate in lung tissue as well as lymph nodes[68]. Asbestos fibers have also been identified in the pleura following autopsy[69] and in the parietal pleural in samples collected during thoracoscopy[70]. Tissue asbestos measurements consistently show that chrysotile asbestos is related to human mesothelioma; there have been numerous reports of mesotheliomas in people where chrysotile is the only or vast majority of the fiber present[71]. Fundamentally, it is well recognized and generally accepted that lung tissue fiber burden does not provide an accurate index of prior exposures to chrysotile asbestos. Accordingly, it is generally recognized that a reliable occupational history is the best indicator of past exposures to

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[68] Dodson et al, *Asbestos content of lung tissue, lymph nodes, and pleural plaques from former shipyard workers*, Am Rev Respir Dis, 142: 843–847 (1990); Dodson et al, *Measurements of asbestos burden in tissues*, Ann N Y Acad Sci, 1076: 281–291 (2006).

[69] *E.g.*, Dodson et al, *Asbestos content of lung tissue, lymph nodes, and pleural plaques from former shipyard workers*, Am Rev Respir Dis, 142: 843–847 (1990); Gibbs et al, *Fibre distribution in the lungs and pleura of subjects with asbestos related diffuse pleural fibrosis*, Br J Ind Med, 48: 762–770 (1991); Suzuki et al, *Asbestos tissue burden study on human malignant mesothelioma*, Ind Health, 39: 150–160 (2001).

[70] Boutin et al, *Black spots concentrate oncogenic asbestos fibres in the parietal pleura. Thoracoscopic and mineralogic study*, Am J Respir Crit Care Med 153: 444–449 (1996).

[71] Godwin, *Letter to the Editor: Asbestos and Mesothelioma*, 204 JAMA 151 (1968) (finding that "[a]nalysis of tissue by x-ray diffraction indicated that chrysotile was the only form of asbestos present."); Rogers et al., *Relationship Between Lung Asbestos Fiber Type and Concentration and Relative Risk of Mesothelioma: A Case-Control Study*, 67 CANCER 1912 (1991) (reporting two cases of peritoneal mesothelioma with only chrysotile in their lungs, and two cases of mesothelioma with only chrysotile in their lungs with a history of exposure only to chrysotile.); Roggli et al., *Asbestos Fiber Type in Malignant Mesothelioma: An Analytical Scanning Electron Microscopic Study of 94 Cases*, Am. J. Ind. Med. 23:605-614 (1993) (concluding that "chrysotile along with its contaminant, tremolite – are capable of producing mesotheliomas in humans and experimental animals."); Dufresne et al., *Fibers in Lung Tissues of Mesothelioma Cases Among Miners and Millers of the Township of Asbestos, Quebec*, Am. J. Ind. Med. 27:581-592 (1995) (concluding that chrysotile (and its contaminant tremolite) were likely the cause of several cases of mesothelioma among this population."); Dodson et al., *Asbestos in Extrapulmonary Sites: Omentum and Mesentery*, Chest 117;486-493 (2000) (reporting that "[l]ong fibers of chrysotile reached the omentum in several cases, which indicates that chrysotile is also translocated and could be potentially important in the pathogenesis of peritoneal mesothelioma."); Kohyama et al, *Analysis of Asbestos Fibers in Lung Parenchyma, Pleural Plaques, and Mesothelioma Tissues of North American Insulation Workers*, 643 Ann. N.Y. Acad. Sci. 27 (1991) (finding "fibrotic pleura and/or hyaline plaques of these workers were found to contain mainly chrysotile, the converse was true for the lung parenchyma. . . . [L]arge numbers of chrysotile fibers were detected in the extrapulmonary sites, such as in the pleural plaques and in pleural and peritoneal mesotheliomatous tissues."); Suzuki et al, *Translocation of Inhaled Asbestos Fibers From the Lung to Other Tissues*, AM J. IND. MED. 19:701-704, 702 (1991) (reporting "asbestos fibers detected in [a type of peritoneal fibrosis] were overwhelmingly chrysotile"); Suzuki et al., *Asbestos fibers and human malignant mesothelioma*, in Advances in the Prevention of Occupational Respiratory Diseases, K. Chiyotani et al., eds. (1998) (indicating that "[t]he asbestos type seen in the mesothelial tissue was chrysotile alone in the majority (68/86; 79.0%)."); Suzuki et al, *Asbestos Tissue Burden Study on Human Malignant Mesothelioma*, Ind. Health 39, 150-160 (2001) (on review of lung and mesothelial tissue, the authors reported "[c]hrysotile was the most common asbestos type detected in the mesothelial tissues. It was present in 62 of the 64 cases (96.9%); chrysotile was exclusively detected in 48 of the 62 cases (77.4%)."); Suzuki et al, *Asbestos Fibers Contributing to the Induction of Human Malignant Mesothelioma*, Ann. N.Y. Acad. Sci. 982:160-176 (2002) (finding six cases of mesothelioma (including one case of *peritoneal* mesothelioma) with *solely* chrysotile present in the lung tissue.);

chrysotile[72] and that the absence of chrysotile on digestion, particularly at low magnification, does not provide a basis for concluding that an individual did not have a biologically significant exposure to chrysotile in the past.

Human Case Reports Support the Conclusion that All Types of Asbestos Cause Human Mesothelioma

20. Because the consensus of the mainstream medical and scientific community is that, in North America and elsewhere, mesothelioma is a "signal tumor" or "signature tumor" with essentially one cause – asbestos – the scientific community has long considered individual cases of mesothelioma to be sentinel events. A sentinel event is a case of disease that, when it appears, signals the need for action. In 1983 Rutstein developed a list of Sentinel Health Events ("SHE-O") that are occupationally related[73]. Mesothelioma was included as a sentinel disease for asbestos exposure on the initial list of SHE-O, and has been included in all subsequent revisions. In fact, most asbestos scientists agree that the worldwide acceptance of mesothelioma as an asbestos-related cancer began with the case series published by Wagner in 1960[74]. When examining the question of causation of sentinel diseases like mesothelioma the scientific community recognizes that case reports and case series reports are useful and valid tools.

21. Moreover, unlike many other cancers, for which there are multiple, well-documented causal factors, mesothelioma is overwhelmingly caused by asbestos. "Mesothelioma is a rare cancer with one major etiologic exposure, therefore surveillance using each case as a sentinel event might seem more reasonable for this disease than for cancers with multi-factorial causation[75]."

22. Case series are particularly informative in situations where there are identified occurrences of very rare conditions for which there are few, if any, established causal factors. In fact, recognition of even a small number of cases of the "sentinel" diseases – such as liver angiosarcoma related to vinyl chloride and malignant mesothelioma which is strongly related to asbestos exposure[76].

23. The scientific community has concluded that, for sentinel diseases such as mesothelioma, case series reports can be sufficient by themselves to allow reliable conclusions to be drawn regarding causation. Again, as noted by Checkoway:

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[72] Roggli, et al. *Tremolite and Mesothelioma*, Ann. Occup. Hyg. 5:447-53 (2002).
[73] Rutstein, et al. *Sentinel health events (occupational): a basis for physician recognition and public health surveillance*. Am J Public Health; 73:1054-61 (1983)
[74] Wagner, et al. *Diffuse pleural mesothelioma and asbestos exposure in the North Western Cape Province*. Br J Ind Med [17], 260-271. (1960). Ref Type: Journal (Full)
[75] Teschke, et al. *Mesothelioma surveillance to locate sources of exposure to asbestos*. Can J Public Health; 88(3):163-8 (May 1997).
[76] Checkoway, et al. *Research Methods in Occupational Epidemiology. 2nd ed.* London: Oxford University Press; (2004)

"Case series reports can be virtually conclusive in their own right when the health outcome is a very rare disease or an uncommon manifestation of a relatively common condition[77]."

24. Not surprisingly, the medical literature contains numerous case reports of mesotheliomas caused by as little as a few months, weeks, or even days of asbestos exposure[78]. Over the past several decades many case series of mesothelioma have been published, and some of these reports provide detailed exposure histories for the mesothelioma cases. Many of these cases of mesothelioma have had limited exposure to asbestos, either because the exposure was of a short duration or because it occurred in a scenario unlikely to generate high levels of airborne fibers. For example, Browne and Smither,[79] in a study of 143 cases of mesothelioma, reported that 32 cases were exposed for less than one year, of whom 21 had no more than six months and 9 had no more than three months asbestos exposure. Greenberg and Davies,[80] reporting on cases of documented mesothelioma from a mesothelioma register between 1967-68, found several with short duration of exposure: one case had only 1 day of exposure to sawing asbestos cement sheets; another case had limited household exposure through her husband who worked in an asbestos factory for only two years, and a third had intermittent exposure to asbestos through her brother's work over a 3 year period. Newhouse and Thompson[81] reported 2 cases of mesothelioma with 2 months or less exposure to asbestos in a case series from London. In 1973 Borow[82] reviewed 72 cases, which included 2 mesotheliomas in stock clerks who worked in areas "not heavily contaminated with asbestos" for 10 months and 18 months respectively. In 2001, Neumann described the characteristics of 1600 mesothelioma cases from the

[77] Checkoway, et al. *Research Methods in Occupational Epidemiology. 2nd ed.* London: Oxford University Press; (2004).

[78] *See, e.g.*, K. Browne & W.J. Smither, *Asbestos-related Mesothelioma: Factors Discriminating between Pleural and Peritoneal Sites*, 40 British Journal of Industrial Medicine 145, 147 (1983) (in a study of 143 cases of mesothelioma, 32 cases were exposed for under one year, of whom 21 had no more than six months of exposure and 9 had no more than three months); Morris Greenberg & T.A. Lloyd Davies, *Mesothelioma Register 1967-68*, 31 British Journal of Industrial Medicine 91, 96, 103 (1974) (documenting mesothelioma following an asbestos exposure of 3 weeks in one case and 1 day in another); 1965 Newhouse and Thompson Paper at 267 (documenting 2 cases of mesothelioma with 2 months or less exposure to asbestos); Maxwell Borow et al., *Critical Review, Mesothelioma following Exposure to Asbestos: A review of 72 Cases*, 64(5) Chest 641, 642 (1973) (documenting mesotheliomas in stock clerks who worked in areas "not heavily contaminated with asbestos" for 10 months and 18 months respectively). *See also* National Institute for Occupational Safety & Health, U.S. Department of Health & Human Services, *Workplace Exposure to Asbestos, Review and Recommendations*, Publication No. 81-103, 3 (1980) ("[A]ll levels of asbestos exposure studied to date have demonstrated asbestos-related disease, and a linear relationship appears to best describe the shape of the dose-response curve. These considerations led the committee to conclude that there is no level of exposure below which clinical effects do not occur. Third, the absence of a threshold is further indicated by the dramatic evidence of asbestos-related disease in members of asbestos-worker households and in persons living near asbestos-contaminated areas. These household and community contacts involved low level and/or intermittent casual exposure to asbestos. Studies of duration of exposure suggest that even at very short exposure periods (1 day to 3 months) significant disease can occur.").

[79] Browne, et al. *Asbestos-related mesothelioma: factors discriminating between pleural and peritoneal sites*. Brit J Ind Med;40: 145-52 (1983)

[80] Greenberg, et al. *Mesothelioma register 1967-68*. Br J Ind Med; 31(2):91-104 (Apr 1974)

[81] Newhouse, et al. *Mesothelioma of pleura and peritoneum following exposure to asbestos in the London area*. Br J Ind Med 1993; 50(9):769-78 (Sep 1965).

[82] Borow, et al. *Mesothelioma following exposure to asbestos: a review of 72 cases*. Chest; 64(5):641-6 (Nov 1973)

German mesothelioma registry from 1987-1999, and reported exposure as short as 1 month in one case. (The authors also reported that over 95% of all the cases had an elevated asbestos fiber burden.) Leigh et al have described the characteristics of mesothelioma cases from 1945-2002 from the Australian Mesothelioma Surveillance Program, and report that 3% of cases had exposures shorter than 3 months; the shortest duration of exposure for one case of mesothelioma was 16 hours of loading asbestos fiber on ships[83]. Miller[84] reviewed the details of 32 mesothelioma cases attributed to household exposure; one case lived in the same boarding house as several shipyard workers for 8 years, another was a wife exposed to asbestos on her husband's clothes for only a year, and 3 others had household exposure less than 3 years. Hansen[85] described the pattern of asbestos-related disease in residents of Wittenoom Township in Australia, the location of a large asbestos mine. Twenty-four residents who had never worked in the mine developed mesothelioma by the time of this report; two had lived in Wittenoom for a very short time (6 weeks and 3 months) and had no other identified exposure to asbestos. Ascoli[86] described a series of 79 cases, among whom two cases had exposure to asbestos solely through living or working in a building with asbestos insulation or roofing. Schneider[87] reported a case of mesothelioma with asbestos exposure documented through a fiber burden analysis of the lung; her only exposure to asbestos was working for three years in an office where asbestos has been sprayed onto steel beams exposed in the ceiling, and had no other exposure to asbestos. Chen[88] reported a similar case of mesothelioma in a man whose only exposure to asbestos was on visits to building sites in his role as executive of a building materials firm; asbestos exposure was documented through lung fiber analysis. Lemen (2004) reported, based on a review of the published literature relating to brakes, more than two hundred (200+) cases of mesothelioma in people exposed to chrysotile asbestos from brakes[89]. Consistent with these findings, Welch et. al. published a small case-control study of college-educated men with peritoneal mesothelioma and limited past exposures to asbestos, a finding contrary to the claim that asbestos-related peritoneal mesotheliomas only occur after exposure to amphibole. These cases demonstrate that very limited exposure to asbestos is found in many case series of mesothelioma. Case reports and case series show that mesothelioma occurs in people with exclusively chrysotile exposure or with mostly chrysotile exposure[90]. A recent registry

[83] Leigh, et al. *Malignant mesothelioma in Australia, 1945-2002*. Int J Occup Environ Health; 9(3):206-17 (Jul 2003)
[84] Miller. *Mesothelioma in Household Members of Asbestos-Exposed Workers: 32 United States cases since 1990*. Am J Ind Med; 47:458-62 (2005).
[85] Hansen, et al. *Environmental exposure to crocidolite and mesothelioma: exposure-response relationships*. Am J Respir Crit Care Med; 157(1):69-75 (Jan 1998).
[86] Ascoli, et al. *Malignant mesothelioma in Rome, Italy 1980-1995. A retrospective study of 79 patients*. Tumori; 82(6):526-32 (Nov 1996)
[87] Schneider, et al. *Pleural Mesothelioma Associated with Indoor Pollution of Asbestos*. J Cancer Res Clin Oncol; 127(2):123-7 (2001)
[88] Chen, et al. *Malignant mesothelioma with minimal asbestos exposure*. Hum Pathol; 9(3):253-8 (May 1978).
[89] Lemen, *Asbestos in brakes: exposure and risk of disease*. Am J Ind Med 45(3):229-237 (2004).
[90] Enticknap et al, *Peritoneal Tumours in Asbestosis*, Brit. J. industr. Med., 21, 20 (1964); Godwin et al, *Letter to the Editor: Asbestos and Mesothelioma*, 204 JAMA 151 (1968); Champion, *Two Cases of Malignant Mesothelioma after Exposure to Asbestos*, 103 Am. Rev. Resp. Disease 821 (1971); Borow et al., *Mesothelioma following Exposure to Asbestos: A Review of 72 Cases*, CHEST 64;641-646 (1973)(finding *all* 72 cases of mesothelioma occurred since the mill had been using predominantly chrysotile and that "it has been shown clinically and experimentally that Chrysotile is a factor in the development of mesothelioma."); Acheson et al., *Mortality of two groups of women who*

study identified large numbers of pleural and peritoneal mesotheliomas with low-level chrysotile exposure in the Japanese automobile manufacturing industry.[91]

There is No Safe Exposure to Any Type of Asbestos: Any Exposure Above Background Can Cause Mesothelioma in Humans

25. There is no safe level of exposure to any type of asbestos fiber. This is not a new or novel opinion in the medical and scientific community; rather the literature is replete with physicians and scientists reaching that opinion. In 1956, one asbestos company scientist published his opinion that "it is prudent to set the standard for cancerigenic [sic] substances substantially at zero . . . and no considerations can justify allowing inhalation of any concentration which is avoidable[92]."

26. In 1964, at a major medical conference on asbestos-related disease, another asbestos industry medical officer expressed the opinion clearly and concisely:

> Our own conclusion, as we began seeing what was happening in our own process, was that *the only safe amount of asbestos dust exposure was zero* and that the efforts in terms of achieving that lay basically in engineering, and, secondly, in education. But as far as a safe level of asbestos dust is concerned, our own conclusion in Hogansville, Ga., is that *there is no safe level. The safe level is nil and anything above the safe level represents certain risk*[93]."

This echoes the work of Merewether, et al of several decades earlier[94].

27. Experienced medical and scientific experts continue to agree that there is no safe level of exposure to asbestos. For example, in 2011, the Inspector General for the United States

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manufactured gas masks from chrysotile and crocidolite asbestos: a 40-year follow-up, Br. J. Ind. Med. 39;344-348 (1982) (reporting a case of mesothelioma among employees at a factory that used only chrysotile); Cullen et al, *Chrysotile Asbestos and Health in Zimbabwe: I. Analysis of Miners and Millers Compensated for Asbestos-Related Diseases Since Independence (1980)*, Am. J. Ind. Med. 19:161-169 (1991) (finding two cases of mesothelioma among Zimbabwe chrysotile miners; one confirmed at autopsy and a second probable case); Egilman et al, *Abuse of Epidemiology: Automobile Manufacturers Manufacture a Defense to Asbestos Liability*, Int. J. Occup. Environ. Health 11:360-371 (2005) (reporting new cases of mesothelioma out of a plant using predominantly chrysotile); Egilman et al, *A Case of Occupational Peritoneal Mesothelioma From Exposure to Tremolite-Free Chrysotile in Quebec, Canada: A Black Swan Case*, Am. J. Ind. Med. (2010) (reporting a peritoneal mesothelioma from exposure to asbestos in a chrysotile mine which may not be contaminated with tremolite).

[91] Gemba, et al, *National survey of malignant mesothelioma and asbestos exposure in Japan*, Cancer Sci. 103 (3):483 – 90 (2012)

[92] Smyth, *Improved Communication – Hygienic Standards for Daily Inhalation*, Industrial Hyg. Quarterly 17(2) (1956) (Dr. Smyth was an employee of Union Carbide, which at the time was a major manufacturer of asbestos containing phenolics and which later became a major miner and distributor of asbestos).

[93] Wells, Ann N Y Acad Sci 132 (1)1-766 (1965) (reporting discussion at page 336) (emphasis added).

[94] Merewether et al, *Report on Effects of Asbestos Dust on the Lungs and Dust Suppression in the Asbestos Industry*, HMSO (1930).

Environmental Protection Agency wrote that "[a]sbestos is a human carcinogen with no safe level of exposure[95].

28. Studies show excess of mesothelioma with non-occupational exposures, which are generally understood to be lower doses that occupational exposures. These data in combination with the data that 90% or more of mesotheliomas have either a history of exposure or substantial asbestos in lung tissue, again suggest that the potential of causation by asbestos should be considered for every mesothelioma.

29. A large case-control study by Iwatsubo et al., found an excess of pleural mesothelioma in the lowest exposure group with an estimated total exposure between 0.001 and 0.49 f/ml-yrs. Iwatsubo et al., *Pleural mesothelioma: Dose response relation at low levels of asbestos exposure in a French population-based case-control study*, Am J of Epidem;148:133-142 (1998).

30. Rödelsperger concluded there was a distinct dose-response relationship, even at extremely low levels of asbestos exposure, with exposures from >0 to <0.15 f/cc-yrs showing a significantly increased risk of mesothelioma[96].

31. In the article by Hodgson and Darnton, there is extrapolation information with regards to crocidolite that at cumulative exposure levels of only 0.01 f/ml-yrs, there are 20 deaths per 100,000 exposed with the highest arguable estimate 100 and the lowest 2 cases. Even at the lowest estimate of 2 cases per 100,000 exposed, this would be in excess of 20 times the figure commonly used as an *assumed* level of background or spontaneous mesothelioma development, which is approximately 1-2 cases per million people per year[97]. With respect to amosite, at a level of cumulative exposure of 0.01 f/ml-yrs, the estimate is 3 deaths per 100,000 exposed, with the highest arguable estimate 20 and the lowest insignificant. For chrysotile, the risk for development of mesothelioma at 0.01 f/ml-yrs was stated to be probably insignificant, although the highest arguable estimate was 1 death per 100,000 exposed, which would still be 10 times that of the *assumed* background rate of 1 case per 1,000,000. The authors stated: "Taking this evidence together, we do not believe there is a good case for assuming any threshold for mesothelioma risk[98]."

32. An update by Hodgson and Darnton in 2009 concerning mesothelioma risk from chrysotile asbestos stated that, when information from a number of recent, well-conducted studies was

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[95] USEPA, Office of Inspector General, *Early Warning Report: Use of Unapproved Asbestos Demolition Methods May Threaten Public Health*, Report No. 12-P-0125 (December 14, 2011)

[96] Rödelsperger et al., *Asbestos and man-made vitreous fibers as risk factors for diffuse malignant mesothelioma: Results from a German hospital-based case-control study*, Am J Ind Med 39:262-275 (2001).

[97] One should note that this is an *assumed* level used to allow a standard for comparison. While it is commonly used as a comparison point, as discussed above, several significant papers have failed to find evidence to support *any* measurable "background" incidence of mesothelioma. Strauchen, *Rarity of Malignant Mesothelioma Prior to the Widespread Commercial Introduction of Asbestos: The Mount Sinai Autopsy Experience 1883 – 1910*, Am. J. Industr. Med. 1-3 (2011); Mark et al, *Absence of Evidence for a Significant Background Incidence of Diffuse Malignant Mesothelioma Apart from Asbestos Exposure*, Ann. NY Acad Sci 643:196 – 204 (1991)..

[98] Hodgson JT, Darnton A. The quantitative risk of mesothelioma and lung cancer in relation to asbestos exposure, Ann Occup Hyg; 44:565-601; specifically, Table 11, page 585 (2000).

incorporated into their mathematical model, the risk of mesothelioma caused by chrysotile derived from these data increased by a factor of 10 over the estimate from their earlier meta-analysis. The authors stated these new results strengthened the case for the proposition that the per fiber risk of mesothelioma from chrysotile textile plants was greater than it was in the mines. Whether this applied to other settings of chrysotile was stated to not be clear[99].

33. In an abstract presented at the International Mesothelioma Interest Group Meeting, Rolland et al. evaluated the risk of pleural mesothelioma in a French population-based case-control study between 1998 and 2002. The authors studied 19 French districts within the National Mesothelioma Surveillance Program covering 25% of the French population. The report was based on 467 confirmed cases (80% males, 41-93 years old) and 868 controls matched for sex, age and district. The authors found that among men, the highest risk was observed for the occupations of plumbers, pipefitters, sheet metal workers, and for the industries of ship repair, asbestos products, metal products and construction. The authors stated a significant dose-response relationship was found between cumulative occupational asbestos exposure and pleural mesothelioma, even for the lowest category (greater than 0-0.07 fibers/ml year; odds ratio 2.8, 95%; CI 1.7-4.7)[100].

34. Indeed, the expert *consensus* is that there is no safe level of exposure to asbestos. None of the major scientific bodies that have studied asbestos and mesothelioma have been able to identify a level of asbestos exposure below which mesothelioma will not occur. *See* World Health Organization: "No threshold has been identified for the carcinogenic risk of chrysotile[101]"; National Cancer Institute Fact Sheet, *Asbestos Exposure and Cancer Risk*[102] ("the overall evidence suggests there is no safe level of asbestos exposure); The British Thoracic Society concludes that "a history of occupational asbestos exposure can be obtained in about 90% of cases in the U.K." and there is "no evidence for a threshold dose of asbestos below which there is no risk[103]." A recent study examining the relationship between historical asbestos use and disease rates further supports the conclusion that a linear dose-response relationship exists between exposure to asbestos and disease even at low doses[104]. In fact, the Occupational Health and Safety Administration (OSHA) determined that even at the lowest level of asbestos exposure at which OSHA found it feasible to set a standard in the workplace, 0.1 f/cc, there is significant risk of mesothelioma[105].

35. Several agencies have commented that there is no safe level of exposure to asbestos:

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[99] Hodgson JT, Darnton A. Mesothelioma risk from chrysotile. Occup Environ Med 2009.

[100] Rolland P, et al., Risk of pleural mesothelioma: A French population-based case control study [1998-2002], Cancer 2006; 54: Suppl 1S9, abstract 35.

[101] World Health Organization. *Elimination of asbestos-related diseases*. Geneva, Switzerland: World Health Organization; Report No.: WHO/SDE/OEH/6.03 (2006).

[102] National Cancer Institute. *Factsheet - Asbestos: Questions and Answers*. Bethesda MD, National Institutes of Health. Ref Type: Pamphlet (2003)

[103] British Thoracic Society. *Statement on malignant mesothelioma in the United Kingdom*. Thorax; 56(4):250-65 (2001).

[104] Lin RT, et al. *Ecological association between asbestos-related diseases and historical asbestos consumption: an international analysis*. Lancet; 369(9564):844-9 (Mar 10 2007)

[105] Occupational Safety and Health Administration. *Occupational exposure to asbestos; final rule*. Federal Register; 59:40964-1162 (1994).

a. NIOSH, 1976 (page 92): "excessive cancer risks have been demonstrated at all fiber concentrations studied to date. Evaluation of all available human data provides no evidence for a threshold or a 'safe' level of asbestos exposure."
b. NIOSH, 1980 (page 3): "All levels of asbestos exposure studied to date have demonstrated asbestos related disease…there is no level of exposure below which clinical effects do not occur."
c. USPHS, 1980: "It is important to point out that when a permissible level for exposure (PEL) to a certain carcinogen is set by OSHA, there is no implication that such a level is safe. To the contrary, it is the agency's policy that any occupational exposure to a carcinogen carries with it some risk of disease, even if it cannot be easily or precisely measured."
d. NIOSH, 1986 (page 319): "a linear, no threshold, dose-response relationship…Any asbestos exposure carries with it some increased risk of asbestos related disease."
e. OSHA, 1994 (page 40978): "reducing exposure to 0.1 f/cc would further reduce, but not eliminate, significant risk. The 0.1 f/cc level leaves a remaining significant risk."
f. WHO, 1998 (page 144): "Exposure to chrysotile asbestos poses increased risks for asbestosis, lung cancer and mesothelioma in a dose-dependent manner. No threshold has been identified for carcinogenic risks."
g. WTO, 2000: "…the experts confirm the position of the European Communities according to which it has not been possible to identify any threshold below which exposure to chrysotile would have no effect. The experts also agree that the linear relationship model, which does not identify any minimum exposure threshold, is appropriate for assessing the existence of a risk. We find therefore that no minimum threshold level of exposure or duration of exposure has been identified with regard to the risk of pathologies associated with chrysotile, except for asbestosis."

36. The introduction of *any* source of asbestos, above the trace background amounts, into the environment causes a significant increase in the risk of mesothelioma. For example, a recent article examining the incidence of mesothelioma in six Egyptian neighborhoods surrounding a plant that used chrysotile asbestos found 83 cases representing a "26-fold excess risk of pleural mesothelioma due to environmental exposure[106]." The levels of asbestos in these neighborhoods were very low – 17 of the mesothelioma cases occurred in a neighborhood a half a mile away from the plant where airborne asbestos the dust was measured at 0.04 f/cc. An additional 27 mesothelioma cases occurred in neighborhoods between 1 and 2.5 kilometers away with a dust measurement of 0.025 f/cc or less. Other studies have shown similar risks. Azuma[107] compared mesothelioma rates and environmental exposure levels at different periods in Japan and predicted that the "cumulative number of deaths from mesothelioma due to environmental asbestos

[106] Madkour, et al. *Environmental exposure to asbestos and the exposure-response relationship with mesothelioma.* East Mediterr Health J; 15(1): 25-38 (Jan 2009)
[107] Azuma, et al. *Mesothelioma risk and environmental exposure to asbestos: past and future trends in Japan.* Int J Occup Environ Health; 15(2): 166-72 (Apr 2009)

exposure would be around 13,000-30,000 by 2039"; a study by Pan supported the hypothesis that residential proximity to naturally occurring deposits of asbestos in California is significantly associated with an increased risk of mesothelioma[108]. The United States Environmental Protection Agency has noted that, because of the nature of asbestos and its interaction in the human body, each exposure increases the likelihood of developing an asbestos-related disease[109].

37. Attempts to postulate thresholds or safe levels for exposure to asbestos have been dismissed as "logical nonsense[110]." The lack of a defined "safe" level for exposure to asbestos is supported by research, including both epidemiology and medical journal reports. For example, a large French study recently concluded that substantial excess mortality occurs at exposure levels below current regulatory levels[111,112]. The National Research Council Committee on Non-Occupational Health Risks of Asbestiform Fibers found background environmental exposure of 0.0004 f/cc over a 73 year lifetime (which results in a cumulative dose of 0.03 f/cc-y) was associated with 9 cases of mesothelioma per million. A "higher" exposure of 0.002 fibers/cc (which results in a cumulative dose of 0.146 f/cc-y) was associated with 46 cases of mesothelioma per million – a five-fold risk[113]. A recent study examining the relationship between historical asbestos use and disease rates further supports the conclusion that a linear dose-response relationship exists between exposure to asbestos and disease and that no "safe" level of exposure exists[114].

38. Studies of duration of exposure suggest that even at very short exposure periods (1 day to 3 months) significant disease can occur."[115] Expert consensus is that studies have shown that any identified occupational, domestic, or environmental exposure to asbestos increases the risk of mesothelioma[116,117,118].

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[108] Pan, et al. *Residential Proximity to Naturally Occurring Asbestos and Mesothelioma Risk in California.* Am J Respir Crit Care Med (2004); 172:1019-25 (2005)
[109] Environmental Protection Agency. *A Guide for Ship Scrappers: Tips for Regulatory Compliance.* Environmental Protection Agency; Report No.: 315-B-.00-001 (2000).
[110] Hodgson, et al. *The quantitative risks of mesothelioma and lung cancer in relation to asbestos exposure.* Ann Occup Hyg; 44(8):565-601 (Dec 2000).
[111] Iwatsubo, et al. *Pleural mesothelioma: dose-response relation at low levels of asbestos exposure in a French population-based case-control study.* Am J Epidemiol; 148(2):133-42 (Jul 15 1998). Indeed, Iwatsubo et al (1998) found that attempts to quantify the minimum dose of asbestos that will result in mesothelioma through epidemiology have demonstrated that "[a] significant excess of mesothelioma was observed far below the limits adopted in most industrial countries during the 1980s."
[112] Rodelsperger, et al. *Asbestos and man-made vitreous fibers as risk factors for diffuse malignant mesothelioma: results from a German hospital-based case-control study.* Am J Ind Med; 39(3):262-75 (Mar 2001).
[113] Asbestiform Fibers Nonoccupational Health Risks, Committee on Non-Occupational Health Risks of Asbestiform Fibers, Board on Toxicology and Environmental Health Hazards, Commission on Life Sciences, National Research Council, National Academy Press, Washington, D.C. (1984).
[114] Lin RT, et al. *Ecological association between asbestos-related diseases and historical asbestos consumption: an international analysis.* Lancet; 369(9564):844-9 (Mar 10 2007).
[115] National Institute for Occupational Safety and Health. *Workplace Exposure to Asbestos: Review and Recommendations: NIOSH/OSHA Asbestos Work Group Recommendations.* Department of Health and Human Services; Report No.: 81-103 (1980)
[116] Pan, et al. *Residential Proximity to Naturally Occurring Asbestos and Mesothelioma Risk in California.* Am J Respir Crit Care Med (2004); 172:1019-25 (2005)
[117] Iwatsubo, et al. *Pleural mesothelioma: dose-response relation at low levels of asbestos exposure in a French population-based case-control study.* Am J Epidemiol; 148(2):133-42 (Jul 15 1998).
[118] Rodelsperger, et al. *Asbestos and man-made vitreous fibers as risk factors for diffuse malignant mesothelioma: results from a German hospital-based case-control study.* Am J Ind Med; 39(3):262-75 (Mar 2001).

39. In determining cause and effect, physicians and scientific researchers typically look at two distinct issues, general causation and specific causation. General causation focuses on the issue of whether a particular substance is capable of causing a particular injury or condition in the general population. Specific causation, on the other hand, addresses the issue of whether an exposure to a substance or substances has caused or contributed to the development of a particular individual's injury or disease. To determine general causation, researchers evaluate a variety of data sets including animal studies, toxicology studies, molecular studies, case reports, epidemiologic case-control and cohort studies and general biologic principles. If a review of these data sets establishes that there is a general cause and effect relationship, physicians then determine specific causation by ascertaining whether an exposure caused or contributed to a particular individual's disease. This affidavit is limited to a discussion of general causation and how scientists apply general causation concept in making the link between a substance and an injury.

40. As an overall model for determining causality, the considerations espoused by Sir Austin Bradford Hill are well accepted and have been widely used by epidemiologists and scientists of other disciplines[119]. They are: temporality, biologic gradient (dose-response), consistency, biologic plausibility, strength of association, analogy, experimental evidence, coherence and specificity. The scope of medical evidence that substantiate these considerations is both comprehensive and widely inclusive of all the available data. The empirical support for the considerations over such a large epistemological landscape represents, in itself, the ultimate merit of the considerations. While respected as a framework for determining causation, each of Hill's considerations has been subject to criticism.

41. The fact that any one consideration or piece of scientific evidence can always be subject to criticism reinforces the need for consideration of all forms of scientific evidence. As Hill noted, "None of my nine view points can bring indisputable evidence for or against the cause-and-effect hypothesis, and none can be required as a *sine qua non*." Before applying this framework to the issue of whether exposure to chrysotile asbestos causes or contributes to cause mesothelioma, it is important to reflect upon the relative significance of each of these considerations in making such a determination. None of Hill's considerations require epidemiologic data in the sense that that term is used to describe statistical analysis to the exclusion of observational epidemiology.

42. Lemen (2004), using the Bradford Hill considerations, reviewed the evidence for chrysotile's ability to cause mesothelioma and concluded that chrysotile exposure increased the risk of mesothelioma in humans[120]. IARC's most recent review also concludes, using the Bradford Hill considerations, that chrysotile is a cause of pleural and peritoneal mesothelioma, lung cancer and asbestosis, among other diseases[121]. When it comes to looking at cause and effect through epidemiology, IARC noted important limitations:

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[119] Hill, The Environment and disease: association or causation? 58(5) Proc. Royal Soc'y Med. 295, 299 (1965)
[120] Lemen, *Chrysotile Asbestos as a Cause of Mesothelioma: Application of the Hill Causation Model*, Int J Occup Environ Health 10:233–239 (2004).

[121] IARC. Monograph 100C: *Asbestos (Chrysotile, Amosite, Crocidolite, Actinolite And Anthophyllite)*, Lyon: International Agency for Research on Cancer (2012)

> It is important to note that evidence of lack of carcinogenicity obtained from several epidemiological studies can apply only to the type(s) of cancer studied, to the dose levels reported, and to the intervals between first exposure and disease onset observed in these studies. Experience with human cancer indicates that the period from first exposure to the development of clinical cancer is sometimes longer than 20 years; latent periods substantially shorter than 30 years cannot provide evidence for lack of carcinogenicity.

43. "Strength of association" is a reflection of the power of a study. Human epidemiologic studies are not the only source of information type of data available to access this consideration. This consideration can be determined from human, animal or microbiologic studies. The relevance of this consideration is limited by the prevalence of co-factors that may interfere with the measurement of the factor that is being studied. Strength of association is not a measure of the importance of a particular factor in causation[122]. It is a gauge of potential errors due to confounding or bias. Studies with large rate ratios are less likely to contain errors attributable to bias or confounding. Causal factors with "relatively low rate ratios" may be equally or more important than strong associations from a public health perspective. In addition, a rate ratio of two is not required to establish that a factor contributed to a disease in a particular individual (specific causation). For example, chronic smoking of less than a pack a day induces less than a two fold increase in the risk of heart disease. Nonetheless, it is a universal opinion of physicians that smoking contributes to a smoker's heart disease if he/she smoked at this rate. In fact smoking is a contributing cause of death for about 400,000 people annually but "only" contributes to fewer than 100,000 cases of lung cancer each year. The same is true of second-hand or environmental tobacco smoke. The consensus of the medical community is that second-hand smoke causes cancer and other diseases notwithstanding the fact that the pooled risk estimate of the risk of lung cancer caused by second hand smoke is approximately 1.3.[123] Most elevations of blood cholesterol that require medical treatment do not double the risk of heart disease. Furthermore, physicians, when treating a patient for a heart attack, will indicate that previous smoking of a half pack of cigarettes per day for 30 years, family history of heart disease (non-genetic), history of elevated cholesterol of 250 mg/dl are all contributing causes of their patient's heart attack. Considered by themselves, none of these factors have an elevated rate ratio greater than two. Epidemiological studies can, when evaluated together, provide more confidence in an association even in the absence of a "statistically significant" finding from any individual study. Greenland states,

> *...lack of 'statistical significance' is not evidence of a lack of hazard... a claim by an expert that 'statistical significance' or 'nonsignificance' demonstrates presence or*

[122] Rothman, K. J. Causal Inference --- Lanes, S. F.: Error and uncertainty in causal inference. In Causal Inference, pp. 182-183

[123] U.S. Department of Health and Human Services. *The Health Consequences of Involuntary Exposure to Tobacco Smoke: A Report of the Surgeon General.* Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, Coordinating Center for Health Promotion, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, (2006) (Surgeon General finding that a 20-30% increase in risk was sufficient to infer causation of lung cancer from secondhand tobacco smoke at p. 445).

absence of causation should serve as a warning to the court that said expert is incompetent in the use of statistics for causal inference[124].

44. Consider, for example, five different political polls that indicate that one of the candidates for office is ahead by between two and three points, a finding that is within the "sampling error" of each individual poll (non-statistically significant in each individual poll). It would be reasonable to conclude that the candidate was going to win on a more likely than not basis, since there are other types of statistical analysis that allow for such conclusions.

45. Recent epidemiologic studies have showed strong associations between chrysotile asbestos and mesothelioma[125].

46. After delineating each of his nine points, Hill's final emphasis placed responsibility on scientists for making causal judgments without blind (in fact without any) reliance on "statistical tests."

47. Hill explained his consideration as follows:

> *What they* [Hill's nine points] *can do, with greater or less strength, is to help us to make up our minds on the fundamental question- is there any other way of explaining the set of facts before us, is there any other answer equally, or more, likely than cause and effect?* ***No formal tests of significance can answer those questions.*** *Such tests can, and should, remind us of the effects that the play of chance can create, and they will instruct us in the likely magnitude of these effects. Beyond that they contribute nothing to the 'proof' of our hypothesis.... The question that I had to answer, by the use of the National Health Insurance records of that time* [1930], *was this: Do the workers in the cardroom of the spinning mill, who tend the machines that clean the raw cotton, have a sickness experience in any way different from that of other operatives in the same mills who are relatively unexposed to the dust and fibre that were features of the cardroom? The answer was an unqualified 'Yes.' From age 30 to age 60 the cardroom workers suffered over three times as much from respiratory causes of illness whereas from non-respiratory causes their experience was not different from that of the other workers. This pronounced difference with the respiratory causes was derived not from abnormally long periods of sickness but rather from an excessive number of repeated absences from work of the cardroom workers.*

[124] See Declaration of Professor Sander Greenland, taken on June 11, 2001.

[125] *E.g.*, Elliott et al, *Lung cancer mortality in North Carolina and South Carolina chrysotile asbestos textile workers*, Occup Environ Med doi:10.1136 (2012); Loomis et al, *Lung cancer mortality and fiber exposures among North Carolina asbestos textile workers*, Occup Environ Med. 66:535–542 (2009); Mirabelli et al, *Excess of mesotheliomas after exposure to chrysotile in Balangero, Italy*, Occup Environ Med. 65:815–819 (2008); Mamo et al, *Mortality experience in an historical cohort of chrysotile asbestos textile workers*, WS-E-03. Paper presented at the Global Asbestos Congress, Waseda University, Tokyo, Japan, November 19–21, 2004.

> *All this has rightly passed into the limbo of forgotten things. What interests me today is this: My results were set out for men and women separately and for half a dozen age groups in 36 tables. So there were plenty of sums. Yet I cannot find that anywhere I thought it necessary to use a test of significance. The evidence was so clear-cut, the differences between the groups were mainly so large, the contrast between respiratory and non-respiratory causes of illness so specific, that no formal tests could really contribute anything of value to the argument. So why use them?*
>
> *...some editors of journals will return an article because tests of significance have not been applied. Yet there are innumerable situations in which they are totally unnecessary-because the difference is grotesquely obvious. ...*
>
> *Of course I exaggerate. Yet too often I suspect we waste a deal of time, we grasp the shadow and lose the substance. We weaken our capacity to interpret data and to take reasonable decisions whatever the value of P. And far too often we deduce 'no difference' from 'no significant difference.' Like fire, the chi square test is an excellent servant and a bad master*[126].

48. Hill recognized that decisions have to be made in the absence of perfect data noting:

> All scientific work is incomplete--whether it be [sic] observational or experimental. All scientific work is liable to be upset or modified by advancing knowledge. That does not confer upon us a freedom to ignore the knowledge we already have, or to postpone the action that it appears to demand at a given time.

49. It is in this context that the mainstream scientific community has reviewed the literature on asbestos and concluded that asbestos from any source is a cause of mesothelioma in someone with cumulative exposure beyond that of the background exposures sustained by all[127].

50. It is precisely because we understand the limitations of epidemiology and how certain factors can bias studies toward a lack of statistical significance or finding of a point estimate of no increased risk that we look at the epidemiology of a substance along with the other scientific data described above. Each epidemiological study must be evaluated for its strengths and weaknesses and decisions about cause and effect should only be made on reliable data.

51. It is specifically because the epidemiological and other evidence that chrysotile asbestos causes mesothelioma is so strong that the mainstream scientific community has concluded and I am able to conclude that a mesothelioma in a patient exposed to dust from chrysotile asbestos brakes or clutches was caused, in whole or in part, by that dust.

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[126] Hill, *The Environment and disease: association or causation?* 58(5) Proc. Royal Soc'y Med. 295, 299 - 300 (1965) (bold and italics added).

[127] In this regard, all identifiable exposures of an individual are beyond "background" as a matter of simple logic as they are in excess of the "background" exposures of that individual. It is a logical impossibility to measure the risk created by "background" exposures sustained by all individuals as there is no unexposed comparison group against which to measure the rate of disease. Put another way, it is fallacious to say that "background" exposures to asbestos are free from danger – the risk of such exposures simply cannot be measured on a population basis.

52. Scientists do not require epidemiological studies of every job category or every product to conclude that the toxic ingredient caused a signature injury of that toxin[128]. As Dr. Selikoff so poignantly stated, "[t]he floating fibers do not respect job classifications[129]." For example, scientists and physicians will have no trouble linking an individual lung cancer to cigarettes in a 5 year Marlboro smoker, even though there are no epidemiological studies of Marlboro-only smokers, even though we know that different cigarettes have different ingredients and even though that individual also smoked Winston, Pall Mall and or other brands at various other points in their life. Similarly, it's unlikely that a physician would think twice about attributing a poisoning death to arsenic in coffee even though there are no epidemiologic studies of people who ingested arsenic in coffee. Thus, even though there are no well-designed epidemiological studies of workers who worked with chrysotile asbestos joint compounds, the mainstream medical and scientific community would have no trouble attributing the patient's mesothelioma to this chrysotile exposure.

53. Due to the extensive and longstanding use of asbestos, the ambient air in the United States contains minute amounts of asbestos. These ambient air concentrations are generally known as the "background level" and have been reported in United States cities to range from 0.00000001 to 0.0001 f/cc PCM levels in urban areas may be an order of magnitude higher than those in rural areas[130].

54. With respect to background concentrations, it is my opinion that "background" is a vague term that has not been well defined. Regardless of the actual background experienced by any person, any inhalation of asbestos released from a point source would be above background by definition.

55. In 1999 Hillerdal reported several cases of low level exposure to asbestos and the development of mesothelioma and concluded there might not be a true background rate at which mesothelioma occur[131]. Studies have confirmed that mesothelioma is a relatively new disease and appears to correlate with the rise in usage of asbestos[132,133].

56. There is published evidence that environmental asbestos exposures can be sufficient to cause mesothelioma. For example, in a study carried out in greater Cairo, Egypt concerning asbestos and the exposure-response relationship with mesothelioma, the study evaluated the prevalence of malignant pleural mesothelioma due to occupational and environmental (non-occupational) exposure to asbestos among persons who worked in the asbestos manufacturing plant and in persons living in an area nearby the plant. Eighty-eight cases of mesothelioma

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[128] Lemen, *Asbestos: Risk Assessment, Epidemiology, and Health Effects*, Boca Raton: Taylor and Francis (2006).

[129] Selikoff, et al, *Asbestos Exposure and Neoplasia*, JAMA 22- 26 (1964).

[130] U.S.Public Health Service, U.S.Department of Health & Human Services. Toxicological profile for asbestos. Atlanta: Agency for Toxic Substances and Disease Registry; 2001.

[131] Hillerdal G. Mesothelioma: cases associated with non-occupational and low dose exposures. Occup Environ Med 1999;56:505-513.

[132] Mark et al, *Absence of Evidence for a Significant Background Incidence of Diffuse Malignant Mesothelioma Apart from Asbestos Exposure*, Ann. NY Acad Sci 643:196 – 204 (1991).

[133] Strauchen, *Rarity of Malignant Mesothelioma Prior to the Widespread Commercial Introduction of Asbestos: The Mount Sinai Autopsy Experience 1883 – 1910*, Am. J. Industr. Med. 1-3 (2011).

were diagnosed, 87 in the exposed group. The risk of mesothelioma was stated to be higher in the environmentally exposed group than in other groups and was higher in females than males. The prevalence of mesothelioma increased with increased cumulative exposure to asbestos[134]. Pan et al. found that residential proximity to naturally occurring asbestos showed an independent and dose-response association with mesothelioma risk[135]. Goldberg et al. stated: "there is a real burden of environmental asbestos exposure in industrialized countries that could account for approximately 20% of all mesotheliomas." However, further research was needed. Furthermore, the authors stated the high proportion of female mesothelioma cases with no identifiable asbestos exposure suggested that the burden of environmental asbestos exposure was far from negligible[136]. Therefore, based on the information available, all occupational and bystander exposures to asbestos above the background or ambient levels of asbestos within the latency period have the ability to contribute to the causation of mesothelioma.

57. I believe that there is a background/ambient level of asbestos exposure which exists in the environment and I do not believe that background/ambient levels of exposure can be proven to cause mesothelioma by the method of comparative epidemiology. However, if a person sustains asbestos exposures above background/ambient levels of exposure and goes on to develop mesothelioma it is my opinion that all of the exposures above background are significant contributing causes in the development of the mesothelioma. Nevertheless, it is generally accepted in the scientific community that there is no known level of asbestos exposure that has been shown not to contribute to the development of mesothelioma.

58. In January of 1997, a group of 19 experts from 8 different countries met in Helsinki, Finland "to discuss disorders of the lung and pleura in association with asbestos and to agree upon state-of-the-art criteria for their diagnosis and attribution with respect to asbestos." These experts included pathologists, radiologists, occupational and pulmonary physicians, epidemiologists, toxicologists, industrial hygienists, and clinical and laboratory scientists specializing in tissue fiber analysis. Collectively, the group had "published over 1,000 articles on asbestos and associated disorders[137]."

59. In rendering criteria on the attribution of mesothelioma to asbestos exposure, the Consensus Panel considered the following generally accepted concepts regarding mesothelioma:

- The great majority of mesotheliomas are due to asbestos exposure.
- Mesothelioma can occur in cases with low asbestos exposure. However, very low background environmental exposures carry only an extremely low risk.

[134] Madkour et al, *Environmental exposure to asbestos-response relationship with mesothelioma*, Eastern Mediterranean Health J. 15:25–38 (2009)
[135] Pan XL et al. Residential proximity to naturally occurring asbestos and mesothelioma risk in California. Am J Respir Crit Care Med 2005;172:1019-1025.
[136] Goldberg S, Rey G, Luce D, et al. Possible effect of environmental exposure to asbestos on geographical variation in mesothelioma rates. Occup Environ Med 2010;67:417-421.
[137] *Consensus Report: Asbestos, asbestosis, and cancer: the Helsinki criteria for diagnosis and attribution*, Scand J Work Environ Health, 23:311-6 (1997) ("Consensus Report").

- About 80% of mesothelioma patients have had some occupational exposure to asbestos, and therefore a careful occupational and environmental history should be taken.

- An occupational history of brief or low-level exposure should be considered sufficient for mesothelioma to be designated as occupationally related.

- A minimum of 10 years from the first exposure is required to attribute the mesothelioma to asbestos exposure, though in most cases the latency interval is longer (e.g., on the order of 30 to 40 years).

Consensus Report, at p. 313. Relying on these medical facts, the Consensus Panel concluded that "all types of malignant mesothelioma can be induced by asbestos, with the amphiboles showing greater carcinogenic potency than chrysotile" and that "a history of significant occupational, domestic, or environmental exposure to asbestos will suffice for attribution." *Id.* Significantly, the Helsinki Criteria does not require a quantitative estimate of a patient's asbestos "dose" exceeding some undefined level in order to attribute mesothelioma to a given asbestos exposure. The Helsinki Consensus conclusion is that chrysotile asbestos causes mesothelioma.

60. Given the strong possibility that all mesotheliomas are related to asbestos exposure, it is no surprise that the Helsinki criteria stated: "very low background environmental exposures carry only an extremely low risk[138]." Low risk is not zero and any addition to the background exposure is significant.

61. As set forth in Welch et al (2007), the mainstream approach to causation in individual is as follows:

> Examining the question of causation of disease in an individual generally involves four questions: 1) was the individual exposed to a toxic agent 2) does the agent cause the disease present in the individual; 3) was the individual exposed to this substance at a level where disease has occurred in other settings; and 4) have other competing explanations for the disease been excluded?
>
> There is no reasonable dispute regarding Question 2—asbestos causes mesothelioma. Additionally, there are no well-accepted competing explanations in North America regarding mesothelioma that must be excluded, resolving Question 4. As a result, when considering the issue of causation of a mesothelioma, once an occupational or para-occupational exposure to asbestos has been established (Question 1), the sole question remaining for examination is whether the exposure or set of exposures of that individual is similar to exposures that have been documented to cause mesothelioma in others— Question 3.
>
> The mainstream scientific community is in consensus regarding the resolution of

[138] Consensus Report, Asbestos, asbestosis and cancer: The Helsinki criteria for diagnosis and attribution. Scand J Work Environ Health 1997;23:311-316.

Question 3. As discussed above, there is no safe level of exposure to asbestos. Even exposure at current regulatory levels results in excess mesotheliomas. Accordingly, the consensus of the scientific community is that any occupational or para-occupational exposure to asbestos— even "brief or low-level exposures"— must be considered causal in an individual with a mesothelioma[139].

62. I do not believe that exposure to a *single* asbestos fiber is at all likely to cause mesothelioma or any other asbestos related cancer. A single asbestos fiber will not cause non-malignant asbestos disease. Nor do I also believe that every *fiber* contributes to the development of mesothelioma. Rather, it is my opinion that every *exposure* to asbestos contributes to cause mesothelioma.

63. Lung cancer and mesothelioma occur when asbestos fibers such as those described above cause genetic errors in epithelial cells lining the airways, or in mesothelial cells that form the lining of the pleural and peritoneal cavities. All the types of asbestos fibers have been shown to cause the chromosomal rearrangements and aneuploid condition that can lead to neoplastic transformation of epithelial and mesothelial cells. Asbestos damages DNA and causes cancers in both animal models and humans.

64. It is clear that multiple errors take place before cells are committed to developing cancerous clones. The damage to DNA can occur as soon as the fibers reach the target cells. In the case of mesothelioma, fibers that are transported to the pleura within hours or days after each exposure are taken up by the mesothelial cells and can rapidly cause genetic errors. If those errors are in genes that control cell growth, the door to the development of cancer has opened.

65. In an individual who has been diagnosed with a cancer, it is clear that multiple mesothelial cells have accumulated a series of genetic errors over years until one of those cells, with the required set of mutations for that individual, loses control of normal growth and grows out as a clone into a deadly malignant mesothelioma. Cells with genetic errors are routinely removed from the body by natural defense mechanisms, but it takes only one epithelial or mesothelial cell with sufficient errors to escape detection and form the clone that brings the individual to the clinic, usually three to five decades after asbestos exposure. Some mesotheliomas have been shown to develop quickly after asbestos exposures, most likely because of an increased susceptibility to developing genetic errors, or because of a reduced capacity to repair genetic damage, or, perhaps very high levels of exposure. Each exposure to asbestos contributes to the development of the disease process, be it lung scarring, lung cancer, or mesothelioma. A few cases of mesothelioma have been reported with less than ten years of latency[140].

66. Asbestos exposure often involves extremely small fibers released and inhaled in enormously high amounts. But these enormously high amounts look, on paper, deceptively small. Even at a so-called "low" exposure rate – e.g., 0.01 fibers per cubic centimeter (f/cc), ten times lower than the current OSHA permissible exposure limit (PEL) of 0.1 f/cc – an unprotected person may inhale as many as 80 fibers per minute, 4,800 fibers per hour, 38,400 fibers per day, and

[139] Welch, et al, *Asbestos exposure causes mesothelioma, but not this asbestos exposure: an amicus brief to the Michigan Supreme Court*. Int J Occup Environ Health 13:318–327 (2007).
[140] Selikoff and Lee, *Asbestos and Disease*, Academic Press p. 265 (1978).

9,600,000 fibers in a 250 day working year. At the current OSHA PEL of 0.1 f/cc, each of these numbers would be magnified by a factor of ten resulting in 800 fibers per minute, 48,000 fibers per hour, 384,000 fibers per day, and 96,000,000 fibers in a 250 day working year. And 0.1 f/cc is currently at the upper limit of occupationally permissible exposure in the United States. Furthermore, it is recognized by OSHA that exposures at a level of 0.1 f/cc-yr, excess cancer deaths will occur[141].

67. As Lemen documents, what some people consider "low level exposures" actually involve surprisingly high numbers of fibers: "Studies conducted by General Motors researchers of brake wear debris demonstrate that 90,000 asbestos fibers per ng remain in that dust [Williams and Muhlbaier, 1980]. Fibers less than 5 mm in length outnumber fibers greater than 5 mm in length by a ratio of 300:1. This translates to approximately 300 billion asbestos fibers greater than 5 mm per g of wear debris and 90 trillion asbestos fibers less than 5 mm[142]." In cases of pleural mesothelioma, the predominant fiber found in the pleura is chrysotile fibers shorter than 5 microns[143].

68. In determining the relative contribution of any exposures to asbestos above background levels, it is important to consider a number of factors, including: the nature of exposure, the level of exposure and the duration of exposure, whether a product gives off respirable asbestos fibers, the level of exposure, whether a person was close to or far from the source of fiber release, how frequently the exposure took place and how long the exposure lasted, whether engineering or other methods of dust control were in place, and whether respiratory protection was used.

69. I utilize a linear dose-response model for risk assessment that has been used by OSHA, NIOSH and other governmental entities for more than two decades, to reach my opinion that a patient's mesothelioma was caused by his/her total and cumulative exposure to asbestos. I rely upon the methodology of attribution espoused in the Consensus Report, Asbestos, Asbestosis, and Cancer: The Helsinki criteria for diagnosis and attribution. Scan J. Work Environ Health, 23:311-6 (1997) as applied to the factual evidence of a patient's exposures.

70. It is my opinion that mesothelioma is a dose-response disease and that the resulting disease is the cumulative result of the exposures to asbestos that a person receives. The cumulative exposure that a mesothelioma patient has received in his/her lifetime has caused impact to the lungs, has overwhelmed the body's defense mechanisms, brought about genetic changes, and has caused mesothelioma at whatever site it develops.

71. This process takes place as fibers inhaled into the lungs are transported to the pleura and cause injury there, including injury to the mesothelial cells, regeneration of mesothelial cells, and genetic changes to mesothelial cells caused by interaction between the asbestos fibers and the chromosomes of those individual cells. Eventually in a person who develops a mesothelioma,

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[141] See Federal Register, Vol. 51, No. 119, June 20, 1986, Table 6, p. 22644.
[142] Lemen, *Asbestos in brakes: exposure and risk of disease*. Am J Ind Med 45(3):229-237 (2004).
[143] Suzuki et al, *Asbestos Fibers Contributing to the Induction of Human Malignant Mesothelioma*, Ann. N.Y. Acad. Sci. 982:160-176 (2002)

there will be a conversion of one or more of those mesothelial cells to a malignant phenotype, which then eventually grows into a tumor that presents clinically as a mesothelioma.

72. The more asbestos fibers that are inhaled into the lung the more likely it is that more of them will be translocated to the pleura. Of course, some of the fibers inhaled may be removed by the mucociliary escalator, some fibers will be deposited in the alveolar spaces and some may be taken up by macrophages. Other fibers may work their way into the interstitium or make their way to the lymph nodes. But there are fibers from each exposure that make their way to the pleura, which is comprised of mesothelial cells – the target cells for mesothelioma.

73. If a person is exposed to less asbestos fibers, then there will be fewer fibers that ultimately make their way to the pleura. Conversely, if a person is exposed to more asbestos fibers, there will be more fibers that make their way to the pleura. This is the nature of the dose-response relationship between asbestos exposure and mesothelioma: the more asbestos exposure a person has, the greater his/her chance of developing mesothelioma. In a person who develops mesothelioma, that disease is the result of the total and cumulative _exposure_ to asbestos.

Arthur L. Frank MD

SWORN TO AND SUBSCRIBED
before me this 21st day of June, 2012.

Patricia A. Buck
NOTARY PUBLIC

My commission expires: ______

(SEAL)

COMMONWEALTH OF PENNSYLVANIA
NOTARIAL SEAL
PATRICIA A. BUCK, Notary Public
City of Philadelphia, Phila. County
My Commission Expires June 22, 2015